

TOBACCO INDUSTRY RESEARCH COMMITTEE  
150 EAST FORTY SECOND STREET NEW YORK 17, N. Y.

#160

Application For Research Grant

(Cf. #33 activated 2/1/55  
and renewed 2/1/56)

1. Name of Investigator: a) Marion B. Sulzberger, M.D.  
b) Walter Redisch, M.D.  
c) Vincent J. Fontana, M.D.  
d) Kurt De Crinis, M.D.
2. Title: a) Professor and Chairman, Dept. of Dermatology & Syphilology, N.Y. University  
Post-Graduate Medical School; Director, N.Y. Skin & Cancer.  
b) Associate Professor Clinical Medicine, N.Y. U. College of Medicine
3. Institution c) Assistant Clinical Professor Pediatrics, Post-Graduate Medical School  
& Address: d) Research Fellow
- New York University-Bellvue Medical Center  
550 First venue, New York 16, New York
4. Project or Subject:

Investigation of the effects of tobacco on the human vascular system in healthy volunteers as well as in patients with occlusive vascular disease; particular attention to be directed at the possibility that certain tobacco effects are based on peculiar allergic susceptibility of specific individuals rather than upon obligatorily toxic products in tobacco smoke. Also, the possible influence of habitual smoking upon vascular responses is to be ascertained.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

Previous studies by the first-named Applicant (see attached reprints) and by others have shown that extracts of cigarette and other tobacco are capable of producing urticarial reactions in a certain percentage of human beings - and that the incidence of these reactions is higher in:

1. Patients with thrombo-angitis obliterans.
2. Patients with other cardiovascular diseases sometimes associated with smoking.
3. Heavy smokers.

It has also been demonstrated that a significant drop in temperature of the digits during cigarette smoking is demonstrable in about 30% of subjects treated. (Redisch). This figure of approximately 30% corresponds to the approximately 30% of smokers found to react with urticarial reactions to skin tests with tobacco, but it is not known whether it is the same 30% -- i.e. whether those subjects with significant falls in temperature are also those with the urticarial skin responses.

1. The above investigators have found that 15.8% of the 500 individuals skin tested showed positive reactions to one or more of the tobacco extracts. (This figure is in agreement with those published - incidence of allergy in pop.)
2. There were more reactions to the mixed brands of tobacco extract which was not defatted, and fewer reactions to the defatted mixed extract.

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The defatting process would remove an appreciable quantity of esters, aldehydes, and other organic compounds--ordinarily thought to be volatilized in the smoke of the cigarette. This finding suggests that a large number of individuals reacted to this volatile aromatic fraction alone. In the group of positive cases tested, the individuals reacted to from one to five of the extracts. This would indicate that a person positive to tobacco skin test might prove sensitive to only one specific type of tobacco, and not to any other type.

3. Vascular symptoms were reported twice as often in volunteers with positive skin tests to tobacco than in those with negative skin tests.
4. Four times more individuals complained of tobacco symptoms when the tobacco skin tests were positive than when the skin tests were negative.
5. Individuals with positive skin tests to tobacco related twice as much evidence of personal and familial allergy than the negative skin test individuals.
6. Smokers with positive skin tests to tobacco presented four times more tobacco symptoms than those with negative skin tests.
7. Smokers with positive skin tests had  $2\frac{1}{2}$  times more vascular symptoms than smokers with negative skin tests.
8. In non-smokers the incidence of vascular symptoms was about the same whether the skin test was positive or negative.

It is planned to carry out the following experiments to establish whether or not specific allergic sensitization plays a basic role in vascular reactions to tobacco smoking:

- A) Patients with various vascular and other diseases which have sometimes been regarded as being made worse by smoking will be skin tested to ascertain whether their skin reactions are in higher incidence or greater intensity than those of control subjects of equivalent age and exposure to tobacco.
- B) Vascular responses are to be tested by automatic recording of surface temperature and large limb venous occlusion plethysmography, in a constant temperature-humidity room under environmental conditions  $\times$  set at  $20^{\circ}$  and  $25^{\circ}$  C temp. and with 55% humidity. Four groups will be studied:
  - (1) healthy volunteers, smokers;
  - (2) healthy volunteers, non-smokers;
  - (3) patients with occlusive vascular disease, non-smokers.
  - (4) patients with occlusive vascular disease - smokers.ECGs and BCGs before and after smoking will be done in all patients.
- C) The results will be correlated with the results of skin testing and clinical symptomatology.
- D) All the skin test reactions from the battery of tobacco extracts will be statistically analyzed, not only in regard to host factors (such as age, tobacco exposure, smoking, allergic and hereditary constitution, disease, etc.), but also in regard to relative capacity of various brands and types of tobacco to produce sensitization of the vascular tree ("index of sensitization", "relative sensitizing potential").

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6. Budget Plan:

Salaries	\$10,000 per annum
Expendable Supplies	500 " "
Permanent Equipment	1,500
Overhead (20%)	2,500 per annum
Other	500 " "
Total	\$ 15,000

7. Anticipated Duration of Work:

Two years

8. Facilities and Staff Available:

Complete facilities and patients and selected staff of the Departments specified above at the New York Skin and Cancer Unit, University Hospital, Bellevue Hospital, Gouverneur Hospital and other teaching services of New York University-Bellevue Medical Center. Completely equipped circulation laboratory of the New York University Research Service, Goldwater Memorial Hospital with staff of 4 physicians and 2 technicians.

9. Additional Requirements:

Supply of pure tobacco of different types and origin, cigarette tobacco of different brands.

10. Additional Information (Including relation of work to other projects and other sources of supply):

Studies of vascular responses have been carried out in the Medical Center by Walter Redisch, M.D. (N.Y.U. Research Service, Goldwater Memorial Hospital, under the direction of Dr. J. M. Steele) for many years. Dr. Redisch's experience, advice and guidance will be utilized widely in the Study relating to vascular responses. Dr. Vincent J. Fontana's experience and the facilities at the Allergy Laboratory under the direction of Miss Margaret Strauss should prove invaluable in the preparation and control of the tobacco extracts and skin testing.

Signature /s/ Marion B. Sulzberger  
Director of Project

Peter Acokellian (?)  
Business Officer of the Institution  
Business Manager

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